

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Ulrike SCHULZ et al.

Group Art Unit: 1616

Appln. No. : 10/574,219

Examiner: Karpinski, Luke E

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For : AQUEOUS ANTI - PERSPIRATION FORMULATION

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Commissioner for Patents

U.S. Patent and Trademark Office

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Sir:

This Appeal is from the Examiner's rejection of claims 46-48, 50-74, 76 and 77 set forth in the Final Office Action mailed from the U.S. Patent and Trademark Office on November 12, 2010.

A Notice of Appeal in response to the November 12, 2010 Final Office Action was filed on March 14, 2011. A request for a one-month extension of time is being filed concurrently herewith.

The requisite fee under 37 C.F.R. § 41.20(b)(2) for filing this Appeal Brief and the fee for a one-month extension of time are being paid concurrently herewith. The Patent and Trademark Office is hereby authorized to charge any additional fees that may be deemed necessary for maintaining the pendency of this application, including any appeal or extension of time fees that may be deemed necessary, to Deposit Account No. 19-0089.

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I. REAL PARTY IN INTEREST

The real party in interest in this appeal is Beiersdorf AG of Hamburg, Germany.

The corresponding assignment was recorded in the U.S. Patent and Trademark Office on October 3, 2006 at REEL 018443, FRAME 0829.

II. RELATED APPEALS AND INTERFERENCES

An Appeal Brief in related Application No. 11/586,585 was filed on April 8, 2011. An Examiner's Answer was mailed on May 27, 2011. Appellants, Appellants' representative or the Assignee are not aware of any other prior and pending appeals, interferences or judicial proceedings which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

The status of the claims is as follows:

Claims 46-48, 50-74, 76 and 77 are pending in this application.

Claims 1-45, 49 and 75 are cancelled.

Each of claims 46-48, 50-74, 76 and 77 is indicated as rejected in the Final Office Action mailed November 12, 2010.

The rejection of each of claims 46-48, 50-74, 76 and 77 is under appeal. Claims 46-48, 50-74, 76 and 77 involved in the appeal are reproduced in the Claims Appendix attached hereto.

IV. STATUS OF AMENDMENTS

No Amendment has been filed subsequent to the Final Office Action mailed November 12, 2010.

V. SUMMARY OF CLAIMED SUBJECT MATTER

A. Claim 46

Independent claim 46 is drawn to a cosmetic formulation that comprises (a) at least one activated aluminum compound which is effective as antiperspirant, (b) at least one α -hydroxycarboxylic acid which comprises mandelic acid and (c) water. The ratio (a) : (b) is from 15 : 1 to 1 : 1.

See, e.g., page 18, lines 3-12 of the present specification.

B. Claim 68

Independent claim 68 is drawn to a cosmetic formulation that comprises (a) activated aluminium chlorohydrate, (b) mandelic acid and (c) water. The ratio (a) : (b) is from 12 : 1 to 2 : 1.

See, e.g., page 18, lines 3-12 of the present specification.

C. Claim 74

Independent claim 74 is drawn to an aqueous antiperspirant preparation that comprises at least one antiperspirant activated aluminum compound and mandelic acid. The ratio of activated aluminium compound and mandelic acid is not higher than 12 : 1.

See, e.g., page 18, lines 3-12 of the present specification.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The broad issues under consideration are:

1. Whether claims 46-48, 50-61, 64-74, 76 and 77 are properly rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over WO/2003/039505, cited in the instant Office Action as the alleged English equivalent, BANOWSKI et al., U.S. Patent No. 7,294,330 (hereafter “BANOWSKI”), and in particular, whether the disclosure of BANOWSKI is sufficient to establish a *prima facie* case of obviousness of the subject matter of claims 46-48, 50-61, 64-74, 76 and 77.
2. Whether claims 62 and 63 are properly rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over BANOWSKI in view of Gers-Barlag et al., US Patent Publication 2002/0077372 (hereafter “GERS”), and in particular, whether the disclosures of BANOWSKI and GERS are sufficient to establish a *prima facie* case of obviousness of the subject matter of claims 62 and 63.
3. Whether claims 46-48, 50-56, 64-70, 72-74, 76 and 77 are properly rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Shen, U.S. Patent No. 6,042,816 (hereafter “SHEN”), in view of Yu et al., U.S. Patent No. 5,571,841 (hereafter “YU”), and in particular, whether the disclosures of SHEN and YU are sufficient to establish a *prima facie* case of obviousness of the subject matter of claims 46-48, 50-56, 64-70, 72-74, 76 and 77.
4. Whether claims 57-63 and 71 are properly rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over SHEN in view of YU in further view of GERS, and in particular, whether the disclosures of SHEN, YU and GERS are sufficient

to establish a *prima facie* case of obviousness of the subject matter of claims 57-63 and 71.

VII. ARGUMENTS

A. Citation of Authority

Obviousness

The appropriate starting point for a determination of obviousness is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 U.S.P.Q. 459, 466 (1966):

Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.

“A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). The relevant question is “whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue.” *Id.* “We must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention.” *Innogenetics, N.V. v. Abbott Labs.*, 512, F.3d 1363, 1374 n.3 (Fed. Cir. 2008).

“In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant.” *In re*

Rijckaert, 9 F.3d, 1531, 1532 (Fed. Cir. 1993), citing *In re Fine*, 837 F.2d 1071, 1074,5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

“[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) quoted with approval in *KSR Int'l Co. v. Teleflex Inc.* “[T]he analysis that ‘should be made explicit’ refers not to the teachings in the prior art of a motivation to combine, but to the court’s analysis.” *Ball Aerosol & Specialty Container, Inc. v. Ltd. Brands, Inc.* 555 F.3d 984, 993 (Fed. Cir. 2009).

Further, it is also necessary for the Examiner to properly construe what an applied reference *fairly* teaches or discloses. See, e.g., *In re Fracalossi and Wajer*, 681 F.2d 792 (CCPA 1982).

B. Claims 46-48, 50-61, 64-74, 76 And 77 Are Not Properly Rejected Under 35 U.S.C. 103(a) As Being Unpatentable Over BANOWSKI

1. Summary of Rejection

The rejection essentially alleges that the elements of the rejected claims are either disclosed or rendered obvious by BANOWSKI. The rejection concedes that BANOWSKI fails to disclose “an example wherein the claimed components, at the claimed percentages are combined into a single composition” but alleges that BANOWSKI teaches “that all of the claimed components may be combined into a composition within the claimed percentage ranges”. Page 5, second paragraph of the November 12, 2010 Final Office Action.

2. Traverse

a. BANOWSKI discloses a host of β -glucuronidase-inhibiting substances and a host of optional components, resulting in millions of possible combinations

Appellants submit that BANOWSKI teaches hundreds, if not thousands, of substances which are suitable as β -glucuronidase-inhibiting substances that are suitable for use in deodorants and antiperspirants. In particular, in col. 2, lines 8-65 thereof BANKOWSKI states (emphasis added):

The present invention relates to the non-therapeutic use of at least one β -glucuronidase-inhibiting substance chosen from monobasic mono- α -hydroxycarboxylic acids having 2-6 carbon atoms and their physiologically acceptable salts, monobasic polyhydroxycarboxylic acids having 4-8 carbon atoms and 3-7 hydroxyl groups, their intramolecular condensation products as well as ethers thereof with mono-, oligo- and polysaccharides or esters thereof with organic and with inorganic acids as well as the physiologically acceptable salts of these components, polybasic carboxylic acids which are not hydroxy-substituted and have 3-8 carbon atoms and 2-3 carboxyl groups, their esters with optionally alkyl-substituted mono- and oligosaccharides as well as the physiologically acceptable salts of these components, polybasic monohydroxycarboxylic acids having 4-8 carbon atoms and 2-3 carboxyl groups, their esters with optionally alkyl-substituted mono- and oligosaccharides as well as the physiologically acceptable salts of these components, polybasic polyhydroxycarboxylic acids having 4-8 carbon atoms, 2-6 hydroxyl groups and 2-3 carboxyl groups, their esters with optionally alkyl-substituted mono- and oligosaccharides as well as the physiologically acceptable salts of these components, aromatic carboxylic acids having 6-20 carbon atoms, 1-2 phenyl radicals, 1-6 hydroxyl groups and 1 carboxyl group, as well as physiologically acceptable salts thereof, amino acids as well as physiologically acceptable salts thereof, 6,7-disubstituted 2,2-dialkylchromanes or -chromenes, phenolic glycosides with a phenoxy radical substituted at least in the para-position, wherein the substituents are chosen from a methoxy, ethoxy, isopropoxy, n-propoxy, vinyl, methylvinyl, 1-propenyl, 2-propenyl (allyl), isobut enyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, ketopropyl, β -ketobutyl, γ -ketobutyl, β -ketopentyl, γ -ketopentyl and a δ -ketopentyl radical, flavonoids, isoflavonoids, polyphenols, the extracts from green tea (*Camellia sinensis*), from Paraguayan tea (*Ilex paraguayensis*), from Japanese tea (*Camellia japonensis*), from the fruits (berries) of the fan palm or saw palm (Saw Palmetto, *Serenoa repens*), from the leaves of *Gingko biloba*, from apple pips, from the fruits (berries) of *Phyllanthus emblica*, from the leaves of the olive tree (*Olea europaea*), from the bark of the pine tree (*Pinus Pinaster*), from rosemary, from *Bacopa Monniera*, from willow-herb, hyssop, clove, from the blue alga *Spirulina platensis* which has been

enriched with magnesium, and from yeast, monocyclic hydrocarbon compounds having 6-12 carbon atoms, 1-2 hydroxyl groups and oxygen atoms as the only heteroatoms, wherein the ring is formed from 6 or 7 atoms and can be saturated, unsaturated or aromatic, derivatives of phosphonic acid and phosphoric acid chosen from hydroxyethane- 1,1-diphosphonic acid, diethylenetriaminepenta (methylenephosphonic acid), myo-inositol-hexaphosphoric acid (phytic acid) and phosphonomethylated chitosan as well as the alkali metal salts of these components, zinc ricinoleate, geraniol-7 EO as well as soluble inorganic salts of copper(II), zinc and magnesium, in a cosmetic deodorant or antiperspirant composition for reducing the body odor caused by hydrolytic decomposition of steroid esters.

Virtually each of the most diverse classes of compounds mentioned above is discussed in the passage from col. 2, line 66 to col. 9, line 32 of BANOWSKI.

Regarding the aromatic carboxylic acids having 6-20 carbon atoms, 1-2 phenyl radicals, 1-6 hydroxyl groups and 1 carboxyl group BANOWSKI states in the passage from col. 4, line 61 to col. 5, line 9 thereof (emphasis added):

The aromatic carboxylic acids having 6-20 carbon atoms, 1-2 phenyl radicals, 1-6 hydroxyl groups and 1 carboxyl group which are preferred according to the invention and derivatives thereof include mandelic acid, para-hydroxymandelic acid, rosemary acid, ferulic acid, chlorogenic acid, salicylic acid, 2,3-dihydroxybenzoic acid (pyrocatechic acid), 2,4-dihydroxybenzoic acid β -resorcylic acid), 2,5-dihydroxybenzoic acid (gentisic acid), 2,6-dihydroxybenzoic acid γ -resorcylic acid), 3,4-dihydroxybenzoic acid (protocatechuic acid), 3,5-dihydroxybenzoic acid (α -resorcylic acid), gallic acid, the methyl, ethyl isopropyl, propyl, butyl, hexyl, ethylhexyl, octyl, decyl, ethyloctyl, cetyl and stearyl esters and the alkali metal salts of these carboxylic acids. Rosemary acid, ferulic acid and para-hydroxymandelic acid sodium salt are particularly preferred.

Accordingly, even the specific class of compounds that is mentioned as one of many examples of suitable (and structurally most diverse) β -glucuronidase-inhibiting substances and includes mandelic acid, i.e., the class of aromatic carboxylic acids having 6-20 carbon atoms, 1-2 phenyl radicals, 1-6 hydroxyl groups and 1 carboxyl group, includes a total of 13 specific acids and a total of 12 different esters of these acids and a

total of three different alkali metal salts of these acids (if only the Li, Na and K salts are considered), resulting in a total of $13 \times 15 = 195$ different substances as examples of aromatic carboxylic acids having 6-20 carbon atoms, 1-2 phenyl radicals, 1-6 hydroxyl groups and 1 carboxyl group and esters and salts thereof. Of these 195 compounds three compounds (less than 2 %), i.e., rosemary acid, ferulic acid and the sodium salt of para-hydroxymandelic acid, are mentioned as particularly preferred.

It further has to be taken into account that BANOWSKI discloses that cosmetic deodorant compositions which contain a selected β -glucuronidase-inhibiting substance may contain various other, non-essential components such as the hundreds of fat substances, non-polar or polar liquid oils, water-soluble alcohols, hydrophilically modified silicones, surface-active substances, lipophilic coemulsifiers, antiperspirant active compounds and additional deodorants (fragrances, antimicrobial, antibacterial or germ-inhibiting substances, antioxidants or odor absorbents), complexing substances, thickeners and further cosmetically and dermatologically active substances that are disclosed in the passage from col. 10, line 56 to col. 18, line 6 (spanning more than 7 columns) of BANOWSKI.

Antiperspirant active compounds constitute only a small fraction of this host of examples of non-essential components that can be present in the compositions of BANOWSKI. Further, aluminum compounds in turn are only one of several examples of antiperspirant active compounds that may be used according to BANOWSKI. In this regard, it additionally is to be taken into account that the instant claims recite an antiperspirant activated aluminum compound, i.e., not just an (any) antiperspirant

aluminum compound (such as, e.g., aluminum chlorohydrate). In this regard, see also the comments in section VII.B.2.c. below.

Appellants submit that in view of the foregoing facts it cannot reasonably be argued that BANOWSKI teaches a “reasonable number of embodiments which are only directed to deodorant and antiperspirant formulations” as asserted at the bottom of page 15 of the November 12, 2010 Final Office Action, and neither is it seen that BANOWSKI would have prompted one of ordinary skill in the art to provide a composition which comprises both mandelic acid (as β -glucuronidase-inhibiting substance) and an aluminum compound and in particular, an activated aluminum compound as antiperspirant (let alone in the ratios recited in the instant independent claims).

Appellants further note that at the bottom of page 15 of the November 12, 2010 Final Office Action the Examiner alleges that BANOWSKI “also teach[es] hydroxycarboxylic acids as the first beta-glucuronidase inhibiting substance and mandelic acid as the first aromatic carboxylic acid, as well as aluminum chlorohydrate as a preferred antiperspirant salt.”

In this regard, it is pointed out that while BANOWSKI mentions “hydroxycarboxylic acids as the first beta-glucuronidase inhibiting substance”, the hydroxycarboxylic acids first mentioned in BANOWSKI are not aromatic carboxylic acids having 6-20 carbon atoms, 1-2 phenyl radicals, 1-6 hydroxyl groups and 1 carboxyl group but (non-aromatic) mono- α -hydroxycarboxylic acids having 2-6 carbon atoms (see col. 2, lines 10-11 in combination with the sentence bridging columns 2 and 3 of BANOWSKI). In fact, aromatic carboxylic acids having 6-20 carbon atoms, 1-2 phenyl

radicals, 1-6 hydroxyl groups and 1 carboxyl group are mentioned in BANOWSKI only as the sixth example of beta-glucuronidase inhibiting substances.

Also, even if mandelic acid were the first aromatic carboxylic acid mentioned in BANOWSKI, the fact remains that not mandelic acid but rosemary acid and ferulic acid (and para-hydroxymandelic acid in the form of its sodium salt) are mentioned as preferred examples of the class of aromatic carboxylic acids having 6-20 carbon atoms, 1-2 phenyl radicals, 1-6 hydroxyl groups and 1 carboxyl group (and esters and salts thereof).

Even further and as already pointed out above, the instant claims recite an activated aluminum compound and activated aluminum chlorohydrate, respectively, wherefore the Examiner's reliance on "regular" aluminum chlorohydrate is without merit.

In this regard, Appellants note that the fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."); *In re Jones*, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992) (Federal Circuit has "decline[d] to extract from *Merck [& Co. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir. 1989)] the rule that... regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it."). See also *In re Deuel*, 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995). See also MPEP 2144.08.

**b. BANOWSKI neither teaches nor suggests the recited ratio
(a) : (b)**

Regarding the ratios (a) : (b) recited in the instant claims it is pointed out that the most preferred range for the concentration of the (host of) antiperspirant active compounds set forth in col. 15, lines 35-51 of BANKOWSKI is 10-25 wt.% (col. 5, lines 54-58 of BANKOWSKI) and the most preferred range for the concentration of aromatic carboxylic acids having 6-20 carbon atoms, 1-2 phenyl radicals, 1-6 hydroxyl groups and 1 carboxyl group is 0.008 % to 2 wt.% (col. 5, lines 10-15 of BANKOWSKI), which can be calculated to result in a ratio corresponding to (a) : (b) as recited in the instant claims of from 25 : 0.008 to 10 : 2, i.e., from about 3,000 : 1 to 5 : 1 (spanning 3 orders of magnitude).

Accordingly, the overlapping part of the range recited in, e.g., instant claim 46 (15: 1 to 1: 1), i.e., 15 : 1 to 5 : 1 constitutes only a very small fraction (about 0.35 %) of the narrowest range that can be calculated from the respective concentration ranges disclosed by BANOWSKI. The overlapping parts of the ranges for (a) : (b) recited in claims 50, 51, 68 and 74 (i.e., from 12 : 1 to 5 : 1 and from 10 : 1 to 5 : 1, respectively) are even smaller than in the case of claim 46 (about 0.25 % and about 0.15 % of the narrowest range theoretically disclosed by BANOWSKI), wherefore each of these claims is independently patentable, i.e., does not stand or fall together with the remaining claims. It additionally has to be taken into account here that according to claim 68 the ratio recited therein refers to the ratio of two specific substances, i.e., activated aluminum chloride and mandelic acid. Further, claim 67 recites that (b) consists of mandelic acid, i.e., no other α -hydroxycarboxylic acid is present, thereby rendering claim 67 independently patentable as well.

In this regard, it is pointed out that MPEP 2144.05 states, *inter alia* (emphasis added):

"[A] prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). See also *In re Harris*, 409 F.3d 1339, 74 USPQ2d 1951 (Fed. Cir. 2005)(claimed alloy held obvious over prior art alloy that taught ranges of weight percentages overlapping, and in most instances completely encompassing, claimed ranges; furthermore, narrower ranges taught by reference overlapped all but one range in claimed invention). However, if the reference's disclosed range is so broad as to encompass a very large number of possible distinct compositions, this might present a situation analogous to the obviousness of a species when the prior art broadly discloses a genus. *Id.* See also *In re Baird*, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); MPEP § 2144.08.

It further is to be taken into account here that three of the exemplified compositions of BANOWSKI contain aluminum chlorohydrate (not indicated to be activated) and an aromatic carboxylic acid having 6-20 carbon atoms, 1-2 phenyl radicals, 1-6 hydroxyl groups and 1 carboxyl group, i.e., the sprayable translucent antiperspirant microemulsion 2.7 (containing 8 wt.% of aluminum chlorohydrate and 0.01 wt.% of rosemary acid, resulting in a ratio corresponding to (a) : (b) of 800 :1) and two of the antiperspirant roll-ons shown in the second table in col. 23 of BANOWSKI (each of them containing 20 wt.% of aluminum chlorohydrate and about 0.5 wt.% of p-hydroxymandelic acid sodium salt or 0.4 wt.% of salicylic acid, resulting in ratios corresponding to (a) : (b) as recited in the instant claims of about 40:1 and 50:1, respectively).

Accordingly, the only exemplified compositions of BANOWSKI which contain aluminum chlorohydrate (not indicated to be activated) and an aromatic carboxylic acid having 6-20 carbon atoms, 1-2 phenyl radicals, 1-6 hydroxyl groups and 1 carboxyl

group (all different from mandelic acid) show ratios corresponding to (a) : (b) as recited in the instant claims which are far outside the claimed range (by a factor of at least 2.7).

It additionally must be taken into account that the exemplified compositions of BANOWSKI which contain (non-activated) aluminum chlorohydrate and an aromatic carboxylic acid having 6-20 carbon atoms, 1-2 phenyl radicals, 1-6 hydroxyl groups and 1 carboxyl group (all different from mandelic acid) are the only guidance that is provided by BANOWSKI for one of ordinary skill in the art with respect to the ratio that corresponds to the ratio of (a) : (b) as recited in the instant claims because even the most preferred concentration ranges indicated by BANOWSKI for the corresponding classes of compounds leave it completely open which additional components are to be present in a corresponding composition. By way of example, it is apparent that the most preferred concentration range for aromatic carboxylic acids having 6-20 carbon atoms, 1-2 phenyl radicals, 1-6 hydroxyl groups and 1 carboxyl group (and esters and salts thereof) indicated by BANOWSKI applies to not only compositions which additionally contain an antiperspirant (and in particular, an (activated) aluminum compound) but also to, for example, compositions which contain no antiperspirant at all but instead contain, e.g., several of the other substances which may optionally be present in a composition that is encompassed by the disclosure of BANOWSKI (corresponding compositions being exemplified by BANOWSKI).

At any rate, there is no indication whatsoever in BANOWSKI that the ratio that may be considered to correspond to a ratio (a) : (b) as recited in the instant claims is a result-effective variable, wherefore it is not seen that one of ordinary skill in the art would have any reason to try to find optimum ratios within (let alone outside) the

extremely broad range of from about 3,000 : 1 to 5 : 1 that can be calculated on the basis of corresponding most preferred concentration ranges disclosed by BANOWSKI.

c. **BANOWSKI fails to suggest any advantages associated with the use of activated aluminum compounds**

It further is submitted that there is nothing in BANOWSKI which would cause one of ordinary skill in the art to specifically select a combination of mandelic acid and an antiperspirant and in particular, an activated aluminum compound from the thousands of possible combinations encompassed by the disclosure of BANOWSKI. For example and as pointed out above, even if an aromatic carboxylic acid having 6-20 carbon atoms, 1-2 phenyl radicals, 1-6 hydroxyl groups and 1 carboxyl group were to be selected as β -glucuronidase-inhibiting substance, according to col. 5, lines 7-8 of BANOWSKI the preferred acids would be rosemary acid, ferulic acid and parahydroxymandelic acid sodium salt.

Further, while activated aluminum chlorohydrates are mentioned in passing in col. 15, lines 58-61 of BANOWSKI there is no suggestion that these activated chlorohydrates offer any advantage over their "regular" counterparts.

In this regard, the instant specification states at page 4, line 6 to page 5, line 8 and page 7, lines 1-25 (emphasis added):

In order to achieve an increased antiperspirant effectiveness of classic aluminum chlorohydrate (ACH) solutions, these are thermally treated depending on concentration, temperature and pressure, and the resulting solutions are dried by means of spray-drying.

This leads to an increased amount of smaller molecule sizes being present in stable form. However, these activated aluminum complex salts (AACH) effective as antiperspirant disintegrate in water back to their original equilibrium state, meaning that in aqueous preparations increased effectiveness is lost.

Use of these activated ACH types (AACH) has therefore hitherto only made sense in nonaqueous systems since otherwise reconversion to the molecule size distribution as occurs in classic ACH solutions is possible, as described, for example, in the article by A. H. Rosenberg – Antitranspirant Technology, SÖFW-Journal, 128 (4) 2000.

It is therefore an object of the present invention to provide an aqueous preparation which has an increased antiperspirant effectiveness without the described disadvantages. In particular, it is therefore the object to provide aqueous cosmetic preparations which, despite the water content, have an increased antiperspirant effectiveness as a result of the addition of activated aluminum complex salts.

It was surprising and unforeseeable by the person skilled in the art that a cosmetic formulation comprising at least one activated aluminum compound effective as antiperspirant, at least one α -hydroxycarboxylic acid and water permits the provision of a transparent and low-stick cosmetic antiperspirant preparation.

Through the combination of activated aluminum compounds effective as antiperspirant, in particular activated aluminum chlorohydrate (AACH), and at least one α -hydroxycarboxylic acid, preferably mandelic acid, it is possible to prepare aqueous, preferably also transparent cosmetic preparations.

Use of the activated ACH types (AACH) has therefore hitherto only made sense in nonaqueous systems since otherwise reconversion to the molecule size distribution as occurs in classic ACH solutions is possible.

By adding α -hydroxycarboxylic acid, in particular mandelic acid, this reconversion is now surprisingly avoided.

It is assumed that complex formation, for example AACH-mandelic acid, is the cause of this effect.

Thus, a chelate complex could form through aluminum with the alpha-hydroxy group and the acid hydroxy group of mandelic acid with the release of protons. This complex is very stable. Furthermore, the bonding to these two hydroxy groups explains why a gelling according to the invention was observed in the case of mandelic acid.

In addition, the phenyl radicals of mandelic acid can aggregate via the van der Waals forces, thus producing a framework.

In addition, the liberated protons could break open the Al complex, as a result of which water may be incorporated into the helix-like structures of the AACH.

It is decisive that through the combination of α -hydroxycarboxylic acid, in particular mandelic acid, and activated ACH in aqueous media, no destruction of the activation of any kind is observed.

The above statements regarding the lack of stability of activated aluminum antiperspirant salts in aqueous media are confirmed by, e.g., col. 1, lines 14-30 of SHEN.

In other words, the presence of mandelic acid in compositions which comprise an activated aluminum antiperspirant compound and water surprisingly makes it possible to stabilize the activated aluminum compound against decomposition into a “regular” aluminum compound and thus, preserves the increased antiperspirant activity of the activated aluminum compound compared to a “regular” aluminum compound (in this regard see, e.g., bottom of page 10 and top of page 11 of the instant specification). BANOWSKI (and GERS) do not contain the slightest suggestion in this regard, which is yet another reason why BANOWSKI (and GERS) are unable to render obvious the subject matter of any of the instant claims.

Appellants submit that for at least all of the foregoing reasons, BANOWSKI is unable to render obvious the subject matter of any of the instant claims, warranting reversal of the instant rejection.

C. Claims 62 And 63 Are Not Properly Rejected Under 35 U.S.C. 103(a) As Being Unpatentable Over BANOWSKI In View Of GERS

Appellants submit that claims 62 and 63 both depend (ultimately) from claim 46 and thus, are not rendered obvious by BANOWSKI for at least all of the reasons that are set forth above in section VII.B.2. GERS clearly is unable to cure any of the noted

deficiencies of BANOWSKI (and neither has the Examiner made any allegations to the contrary).

D. Claims 46-48, 50-56, 64-70, 72-74, 76 And 77 Are Not Properly Rejected Under 35 U.S.C. 103(a) As Being Unpatentable Over SHEN In View Of YU

1. Summary of Rejection

The rejection essentially alleges, *inter alia*, that SHEN teaches compositions comprising enhanced antiperspirant salts, which allegedly reads on activated antiperspirants, alpha-hydroxycarboxylic acids, and water. The Examiner concedes that SHEN does not teach mandelic acid as hydroxycarboxylic acid but alleges that YU cures this deficiency of SHEN. In this regard, the rejection essentially asserts that YU would have rendered it obvious to one of ordinary skill in the art to produce the formulations of SHEN with mandelic acid as hydroxycarboxylic acid. One of ordinary skill in the art would allegedly have been motivated to do so “because [SHEN] teaches antiperspirant compositions comprising hydroxycarboxylic acids and [YU] teach[es] that alpha-hydroxycarboxylic acids, such as mandelic acid, may be added to antiperspirant formulations to increase efficacy and to reduce wrinkles”. Page 10, second paragraph of November 12, 2010 Final Office Action.

2. Traverse

a. Mandelic acid is not encompassed by the disclosure of SHEN

It is pointed out that the hydroxycarboxylic acids which are to be employed according to SHEN are hydroxy substituted lower alkanoic acids, preferably alkanoic acids having from 2 to 4 carbon atoms in the alkanoic acid chain. This clearly excludes

araliphatic acids such as mandelic acid (in addition, mandelic acid has a total of 8 carbon atoms). In particular, the passage of SHEN relied upon by the Examiner in this regard, col. 6, lines 45-62, states (emphasis added):

The compositions of the present invention also contain a water soluble amino and/or hydroxy acid which is effective in increasing and/or stabilizing the HPLC peak 4:3 area ratio of the antiperspirant salt. Such acids include amino-and/or hydroxy-substituted lower alkanoic acids (including substituted derivatives thereof), preferably where the amino or hydroxy group is located on the α -carbon (i.e. the same carbon to which the carboxy group is attached). The lower alkanoic acid will generally have 2 to 6, preferably 2 to 4, carbon atoms in the alkanoic acid chain. Typical amino and/or hydroxy substituted lower alkanoic acids include any of the amino acids such as glycine, alanine, valine, etc. and hydroxy acids such as glycolic acid and lactic acid. These amino and/or hydroxy substituted lower alkanoic acids may also contain various substituents which do not adversely affect their activity. The preferred amino and/or hydroxy substituted lower alkanoic acids are glycine, alanine, and glycolic acid, with glycine being most preferred.

Appellants note that the only hydroxy substituted lower alkanoic acids having 2 to 6 carbon atoms in the alkanoic acid chain mentioned in the passage of SHEN reproduced above are glycolic acid and lactic acid, i.e., acids having 2 or 3 carbon atoms. The impression that acids with an as low as possible number of carbon atoms are (highly) preferred according to SHEN is reinforced by the fact that the above passage further teaches that glycine (2 carbon atoms) and alanine (3 carbon atoms) are the preferred amino acids, with glycine being the most preferred acid among the amino and/or hydroxy substituted lower alkanoic acids taught by SHEN.

It is submitted that in view of the foregoing facts it cannot reasonably be alleged that SHEN prompts one of ordinary skill in the art to use as amino and/or hydroxy substituted lower alkanoic acid an acid which not only is not a (lower) alkanoic acid but

also contains significantly more carbon atoms (e.g., eight carbon atoms) than the acids which SHEN indicates to be preferred.

Appellants note that at page 17 of the November 12, 2010 Final Office Action the Examiner alleges that “Shen et al. teach preferred acids having 2-4 carbon atoms and do not exclude or teach away from the use of acids with greater than 4 carbon atoms.”

In this regard, it is pointed out that the question here is not whether SHEN teaches away from the use of “acids with greater than 4 carbon atoms” but whether SHEN provides an apparent reason to replace any of the acids which are specifically mentioned (and recommended) by SHEN by an acid which is not even mentioned (let alone recommended) by SHEN, i.e., mandelic acid.

In particular, the only acids which are mentioned in col. 6, lines 45-62 of SHEN as being suitable for use in the compositions taught therein are amino- and/or hydroxy-substituted lower alkanoic acids (including substituted derivatives thereof). Mandelic acid does not even bear a structural resemblance to the acids which are preferred according to SHEN, i.e., glycine, alanine, and glycolic acid (aliphatic acids having (merely) 2 or 3 carbon atoms).

b. YU fails to provide an apparent reason to include mandelic acid in a composition according to SHEN

YU is unable to cure the deficiencies of SHEN noted above. In particular, although YU teaches that the hydroxycarboxylic acids disclosed therein may enhance the therapeutic efficacy of cosmetic or pharmaceutical agents of topically applied agents such

as, *inter alia*, antiperspirants, it must not be forgotten that according to YU hundreds, if not thousands of hydroxycarboxylic acids are suitable for this purpose.

It further is pointed out that glycolic acid and lactic acid, i.e., the two hydroxy-substituted lower alkanoic acids that are most preferred according to SHEN, are not only mentioned in YU as representatives of the hydroxycarboxylic acids taught therein, but are even employed in several of the Examples thereof (see, e.g., Examples 6, 7, 8, 15, 19, 20, 26, and 27 of YU), thereby clearly indicating that the hydroxy-substituted lower alkanoic acids taught by SHEN are also very suitable for the purposes of YU.

In contrast, mandelic acid, while being also mentioned in YU as an example of a suitable hydroxycarboxylic acid for the purposes taught therein, is not employed in any of the 29 Examples of YU. Neither does the list of more than 30 “representative” hydroxy acids in col. 6, lines 24-40 of YU include mandelic acid (although it includes five derivatives of mandelic acid).

Accordingly, even if one of ordinary skill in the art wanted to increase the efficacy of the antiperspirant compositions of SHEN by using a hydroxycarboxylic acid according to YU, there would be no reason to deviate from the teaching of SHEN and to use a hydroxycarboxylic acid which is significantly different from the hydroxycarboxylic acids which are apparently most suitable for the purposes of SHEN. In particular, a comparison of the teachings of SHEN and YU clearly suggests that the hydroxy-substituted lower alkanoic acids which are most preferred according to SHEN would also have the desired efficacy-improving effect taught by YU. In other words, YU fails to prompt one of ordinary skill in the art to use mandelic acid instead of the acids

recommended by SHEN such as glycolic acid or lactic acid as hydroxy-substituted lower alkanoic acid in the compositions of SHEN.

Appellants further note that even if one were to assume, *arguendo*, that YU emphasizes mandelic acid as particularly suitable for treating wrinkles (although it is not seen that the specification of YU provides any support for this allegation or that YU even mentions this alleged property of mandelic acid anywhere other than in the title and in the claims thereof) it is apparent that the ability of a composition to visibly reduce human skin wrinkles (see, e.g., claim 1 of YU) provides no particularly noteworthy benefit for an antiperspirant composition (antiperspirant preparations are applied to the axilla, see, e.g., col. 14, lines 39-44 of SHEN; it is not seen that wrinkle reduction in the axilla is a desirable feature of an antiperspirant composition). At any rate, the ability of reducing wrinkles in the axilla would clearly not be able to outweigh the fact that mandelic acid is significantly different from the hydroxy-substituted lower alkanoic acids which SHEN teaches to be most preferred for the purposes disclosed therein (not taking into account the fact that the acid that is the most preferred acid for the purposes of SHEN is not even a hydroxy-substituted lower alkanoic acid but an amino acid, i.e., glycine, the member of this class of compounds with the smallest number of carbon atoms).

c. One of ordinary skill in the art would be discouraged from using mandelic acid in a composition according to SHEN

Even if one were to assume, *arguendo*, that one of ordinary skill in the art would be motivated to combine the teachings of SHEN and YU for any reason, it is not seen that

he or she would want to use mandelic acid as hydroxycarboxylic acid in the enhanced antiperspirant salts of SHEN.

In particular, as set forth above and as evidenced by col. 6, lines 45-62 of SHEN relied upon by the Examiner, the hydroxycarboxylic acids which are to be employed according to SHEN are hydroxy substituted lower alkanoic acids, preferably alkanoic acids having from 2 to 4 carbon atoms in the alkanoic acid chain. This clearly excludes an araliphatic acid such as mandelic acid.

One of the reasons why SHEN excludes araliphatic acids such as mandelic acid as hydroxycarboxylic acids may be the fact that SHEN requires the use of a soluble calcium salt. See, e.g., claim 1 of SHEN (emphasis added):

A method of stabilizing an aqueous solution of an enhanced efficacy aluminum or aluminum-zirconium antiperspirant salt against rapid degradation of the HPLC peak 4 to peak 3 area ratio of said salt, said method comprising adding to said aqueous enhanced antiperspirant salt solution an effective amount of a soluble calcium salt and an effective amount of a water soluble amino and/or hydroxy acid to form a stabilized aqueous enhanced efficacy antiperspirant salt solution.

However, as can be taken from, e.g.,

http://books.google.com/books?id=Owuv-c9L_IMC&pg=PA618&lpg=PA618&dq=soluble+calcium+mandelate&source=bl&ots=zVs-siTcb&sig=tcChVCOYa24E3XvLMZx1OVO7L9c&hl=en&ei=gi44Sue9F9CptgeA3tXiDA&sa=X&oi=book_result&ct=result&resnum=3 (available on the Internet but not printable)

calcium mandelate is only slightly soluble in water. This is confirmed by, e.g., the disclosure of U.S. Patent No. 4,239,912 (entitled "Process for resolving DL-Mandelic

acid with novel 2-benzylamino-1-butanol"). See EVIDENCE APPENDIX. In the passage from col. 6, line 55 to col. 7, line 5 this patent states (emphasis added):

Racemization and Recovery of DL-Mandelic Acid

The alkalinized aqueous phase from (2) which contains the sodium or potassium salt of the undesired mandelic acid is further alkalinized by the addition thereto of about two moles of additional sodium or potassium hydroxide per mole of mandelic acid therein. The reaction mixture is then heated at reflux until racemization is completed, as indicated by a zero optical rotation. The reaction mixture is then neutralized to pH 7 by the addition of concentrated hydrochloric acid and at least an equivalent amount of calcium chloride is added. The resulting calcium DL-mandelate which precipitates is recovered by filtration, washed with water and reacted in water with an equimolecular amount of sodium carbonate. The precipitated calcium carbonate is recovered by filtration and the resulting filtrate containing sodium DL-mandelate is acidified, as previously described, and recycled in (1).

In the passage from col. 9, line 35 to col. 10, line 4 this patent further states (emphasis added):

EXAMPLE 4

Racemization of Sodium L-(+)-Mandelate

The aqueous solution of sodium L-(+)-mandelate from Example 1 is mixed with 45 mls of 50% aqueous sodium hydroxide, heated to boiling and concentrated to about 1100 mls, then refluxed for 20 hours. At the end of this period the sodium L-(+)-mandelate is completely racemized; $[\alpha]_D^{25} = 0^\circ$ (C, 4 in water).

The solution is then neutralized to pH 7 by adding concentrated hydrochloric acid thereto, and reacted at 50° C. by slowly adding a solution of calcium chloride monohydrate (33 grams; 0.255 mole) in 20 mls of water. The resulting reaction mixture is cooled to 25° C. and filtered to recover the solid. The recovered solid is washed free of chloride ion with water and dried to obtain 79 grams (92.3% of theoretical) of calcium D, L-mandelate.

Accordingly, using mandelic acid in water in combination with a water-soluble calcium salt can reasonably be expected to result in the precipitation of calcium mandelate. This is a clear disincentive rather than a motivation to use mandelic acid for

the purpose disclosed in SHEN and is yet another reason why one of ordinary skill in the art would not use mandelic acid as hydroxycarboxylic acid in the stabilization process disclosed by SHEN.

Appellants note that in this regard the Examiner takes the position that “Shen does not require a complex of said Ca and said hydroxyl acid, there is no requirement in Shen that the inclusion of Ca ions and mandelic acid are from the addition of Ca-mandelate”.
Page 17, third paragraph of the November 12, 2010 Final Office Action.

In response, it is submitted that it is irrelevant in the present context whether or not there is a “requirement” that the Ca ions and mandelic acid are from the addition of Ca-mandelate. Rather, it is apparent to one of ordinary skill in the art that adding both a water-soluble calcium salt (of any acid) and mandelic acid (which according to the Examiner would be selected by one of ordinary skill in the art for increasing and/or stabilizing the HPLC peak 4:3 ratio of the antiperspirant salt of SHEN in view of the teaching of YU) to an aqueous composition according to SHEN would inevitably result in the formation (and likely precipitation) of a Ca salt with an acid that exhibits a lower solubility than the originally employed soluble Ca salt, i.e., calcium mandelate. This has nothing to do with a “requirement” but is a law of nature (chemistry) that one of ordinary skill in the art would be aware of.

Appellants further note that in the Continuation Sheet of the Advisory Action mailed February 1, 2011 the Examiner alleges that “even though Ca mandalate [*sic*] is slightly soluble that still reads on soluble and there is no evidence that the use of Ca and mandelic acid would result in Ca mandalate [*sic*]. While the Examiner agrees that in a simple aqueous formulation said precipitate would form, in complex gel emulsions, as

taught in Shen, there is no way to determine if said precipitation would take place due to the gel structure and plurality of additional components found within the composition.”

In this regard, it is submitted that it is apparent to one of ordinary skill in the art that the meaning of “soluble” in SHEN indeed is “soluble”, not merely “slightly soluble”. After all, according to, e.g., claim 1 of SHEN a stabilized aqueous enhanced efficacy antiperspirant salt solution is to be formed. Further, according to col. 6, lines 37-41 of SHEN, “[g]enerally, the aqueous antiperspirant solution will contain about 0.3 to about 3% by weight Ca, preferably about 0.5 to about 2.5% by weight Ca, most preferably about 1.0 to about 2.0% by weight Ca, based on the weight of the entire composition”. It is apparent to one of ordinary skill in the art that these Ca concentrations cannot be obtained with a “slightly soluble” Ca salt.

Further, while the Examiner agrees that in a simple aqueous formulation a calcium mandelate precipitate would form the Examiner appears to take the position that one of ordinary skill in the art would speculate that in the system disclosed by SHEN a precipitation of Ca mandelate would (possibly) not take place. This is clearly not enough to provide an apparent reason for using mandelic acid in the system of SHEN, the more so since the acids which are identified by SHEN as being suitable are at the same time also acids which are recommended by YU, wherefore there is no reason for one of ordinary skill in the art to use a different acid (mandelic acid) which can reasonably be expected to cause problems at least in terms of the precipitation of a Ca salt.

It is submitted that for at least all of the foregoing reasons, SHEN in view of YU fails to render obvious the subject matter of any of the instant claims, warranting a reversal of the instant rejection.

E. Claims 57-63 And 71 Are Not Properly Rejected Under 35 U.S.C. 103(a) As Being Unpatentable Over SHEN In View Of YU And GERS

Appellants submit that claims 57-63 and 71 depend (ultimately) from claims 46 or 68 and thus, are not rendered obvious by SHEN in view of YU for at least all of the reasons that are set forth above in section VII.D.2. GERS clearly is unable to cure any of the noted deficiencies of SHEN and YU (and neither has the Examiner made any allegations to the contrary).

VIII. CONCLUSION

Appellants respectfully submit that for at least all of the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of any of any of the instant claims over any of BANOWSKI, GERS, SHEN and YU and any combination thereof. The Board is, therefore, respectfully requested to reverse the Final Rejection, and to allow the application to issue in its present form.

Respectfully submitted,
Ulrike SCHULZ et al.

/Heribert F. Muensterer/

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CLAIMS APPENDIX

46. A cosmetic formulation comprising (a) at least one activated aluminum compound which is effective as antiperspirant, (b) at least one α -hydroxycarboxylic acid which comprises mandelic acid and (c) water, a ratio (a) : (b) being from 15 : 1 to 1 : 1.
47. The cosmetic formulation of claim 46, wherein (a) comprises one or more activated aluminum salts.
48. The cosmetic formulation of claim 47, wherein (a) comprises activated aluminum chlorohydrate.
50. The cosmetic formulation of claim 46, wherein the ratio (a) : (b) is from 12 : 1 to 2 : 1.
51. The cosmetic formulation of claim 46, wherein the ratio (a) : (b) is from 10 : 1 to 2.5 : 1.
52. The cosmetic formulation of claim 46, wherein the formulation comprises from 1% to 35% by weight of (a), based on a total weight of the formulation.

53. The cosmetic formulation of claim 52, wherein the formulation comprises up to 25% by weight of (a).

54. The cosmetic formulation of claim 53, wherein the formulation comprises up to 20% by weight of (a).

55. The cosmetic formulation of claim 46, wherein the formulation comprises from 0.1% to 10% by weight of (b), based on a total weight of the formulation.

56. The cosmetic formulation of claim 55, wherein the formulation comprises up to 8% by weight of (b).

57. The cosmetic formulation of claim 46, wherein the formulation comprises an O/W microemulsion.

58. The cosmetic formulation of claim 57, wherein the formulation comprises a microemulsion gel.

59. The cosmetic formulation of claim 58, wherein the formulation comprises an oil-in-water microemulsion which comprises an oil phase, a water phase and less than 20% by weight of one or more emulsifiers, based on a total weight of the microemulsion.

60. The cosmetic formulation of claim 59, wherein the oil phase is essentially composed of constituents of low volatility.

61. The cosmetic formulation of claim 59, wherein the one or more emulsifiers comprise one or more O/W emulsifiers selected from polyethoxylated, polypropoxylated and polyethoxylated and polypropoxylated O/W emulsifiers and one or more optional W/O emulsifiers.

62. The cosmetic formulation of claim 61, wherein the microemulsion is obtained by bringing a mixture comprising the water phase, the oil phase, the one or more O/W emulsifiers and the one or more optional W/O emulsifiers to a temperature within or above a phase inversion temperature range and subsequently cooling the mixture to room temperature.

63. The cosmetic formulation of claim 62, wherein droplets of a discontinuous oil phase are joined together by one or more crosslinker substances whose molecules comprise at least one hydrophilic region which has a size suitable for bridging a distance between the droplets and at least one hydrophobic region which is able to enter into hydrophobic interaction with the droplets.

64. The cosmetic formulation of claim 46, wherein the formulation has a defined yield point.

65. The cosmetic formulation of claim 64, wherein the formulation has a yield point of from 40 to 120 Pa, determined at 25°C by means of a shear stress time ramp of 40 Pa/min.

66. The cosmetic formulation of claim 46, wherein the formulation is suitable for application to human skin.

67. The cosmetic formulation of claim 46, wherein (b) consists of mandelic acid.

68. A cosmetic formulation comprising (a) activated aluminium chlorohydrate, (b) mandelic acid and (c) water, a ratio (a) : (b) being from 12 : 1 to 2 : 1.

69. The cosmetic formulation of claim 68, wherein the ratio of (a) to (b) is from 10 : 1 to 2.5 : 1.

70. The cosmetic formulation of claim 68, wherein the formulation comprises from 1% to 20% by weight of (a) and from 0.1% to 8% by weight of (b), each based on a total weight of the formulation.

71. The cosmetic formulation of claim 70, wherein the formulation comprises an O/W microemulsion.

72. An antiperspirant product which comprises the cosmetic formulation of claim 46.

73. The antiperspirant product of claim 72 which comprises a transparent antiperspirant hydrogel.

74. An aqueous antiperspirant preparation which comprises at least one antiperspirant activated aluminum compound and mandelic acid, a ratio of activated aluminium compound and mandelic acid being not higher than 12 : 1.

76. The cosmetic formulation of claim 46, wherein the formulation is transparent.

77. The cosmetic formulation of claim 70, wherein the formulation is transparent.

EVIDENCE APPENDIX

U.S. Patent No. 4,239,912

(see, e.g., response to Final Office Action mailed November 27, 2009)

RELATED PROCEEDINGS APPENDIX

None.

United States Patent [19]

Halmos

[11] 4,239,912

[45] Dec. 16, 1980

[54] **PROCESS FOR RESOLVING DL-MANDELIC ACID WITH NOVEL 2-BENZYLAMINO-1-BUTANOLS**

[75] Inventor: Imre A. Halmos, Summit, N.J.

[73] Assignee: American Cyanamid Company, Stamford, Conn.

[21] Appl. No.: 968,041

[22] Filed: Dec. 8, 1978

Related U.S. Application Data

[63] Continuation of Ser. No. 831,024, Sep. 6, 1977, abandoned.

[51] Int. Cl.³ C07B 19/00

[52] U.S. Cl. 562/401; 260/501.11; 562/470

[58] Field of Search 562/401, 470; 260/501.11

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Primary Examiner—Natalie Trousof

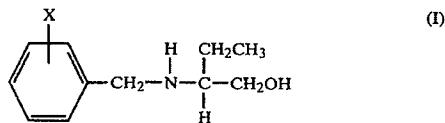
Assistant Examiner—Vera C. Clarke

Attorney, Agent, or Firm—Jack W. Richards

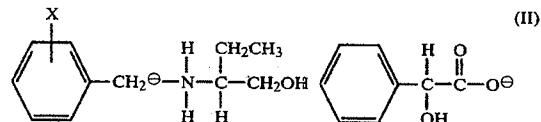
ABSTRACT

A process for resolving DL-Mandelic acid which comprises reacting at moderately elevated temperatures in a

two-phase liquid mixture of water and a suitable water-immiscible organic solvent about equimolecular amounts of DL-Mandelic acid and an optically active 2-benzylamino-1-butanol, represented by formula (I),



to form a crude mandelate salt, represented by formula (II),



wherein X is chloro, bromo, fluoro, or nitro; said crude mandelate salt is recovered and purified by contact with a suitable solvent to obtain an optically pure mandelate salt, represented by formula (II); the optically active mandelate salt is hydrolyzed with aqueous sodium or potassium hydroxide in a two-phase liquid mixture to obtain an organic phase containing an optically active compound of formula (I) and an alkalized aqueous phase containing the sodium or potassium salt of an optically active mandelic acid. The latter is acidified and an optically active mandelic acid is recovered therefrom.

6 Claims, No Drawings

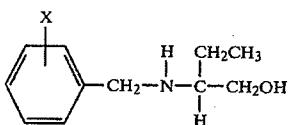
**PROCESS FOR RESOLVING DL-MANDELIC ACID
WITH NOVEL 2-BENZYLAMINO-1-BUTANOLS**

This is a continuation, of application Ser. No. 5 831,024, filed Sept. 6, 1977 now abandoned.

BACKGROUND OF THE INVENTION

The invention relates to a new process for the resolution of DL-Mandelic acid. More particularly, it relates to a process for the resolution of DL-Mandelic acid in a two-phase liquid medium by the use of novel optically active 2-benzylamino-1-butanol.

The novel optically active 2-benzylamino-1-butanol which are useful in this process are represented by Formula (I),



wherein X represents chloro, bromo, fluoro, nitro or methyl. A related pending application, to a process for the resolution of DL-mandelic acid, is U.S. Application Ser. No. 18,695 filed Mar. 8, 1979 which is a continuation application of U.S. application Ser. No. 831,025 filed Sept. 6, 1977 now abandoned.

The use of optically active amines such as quinine, (-)- α -(1-naphthyl)ethylamine, (+)-2-amino-1-butanol, (-)-methylamine, and the like, to resolve racemic mixtures of carboxylic acids, such as tartaric acid, mandelic acid, aspartic acid, and the like, is well known in the art.

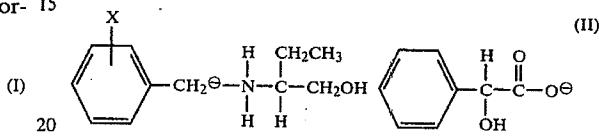
Applicants are not aware of any prior art reference which, in their respective judgements as one skilled in the art of resolving DL-Mandelic acid, would anticipate or render obvious the novel process of the instant invention; however, for the purpose of fully developing the background of the invention and establishing the state of the requisite art, the following references are set forth: Germ. Offen. 2,007,177 which discloses the formation of an optically active ammonium salt by reaction of the dextro- or levo-rotatory 2-(benzylamino)-1-propanol and cleavage of the said ammonium salt with dilute hydrochloric acid to recover the optically active acid. An English language abstract of this reference is contained in Chem. Abs. 73, 120417 (1970). U.S. Pat. No. 3,553,257 which discloses the preparation of dextrorotatory 2-amino-1-butanol. Beilstein 4, 291 which discloses the preparation of levo-rotatory 2-amino-1-butanol.

Since none of the known optically active amines has been found to be completely satisfactory, research continues in order to find new compounds and processes which will be more satisfactory. The present invention arose out of such research and resulted in surprising discovery that racemic mixtures of mandelic acid can be readily resolved in a two-phase liquid mixture of water and a water-immiscible organic solvent with the compounds of formula (I). The process of this invention is useful for the resolution of racemic mixtures of mandelic acid. The utility of D-(-)-mandelic acid and its derivatives, or L-(+)-mandelic acid is known in the art. See, e.g., Germ. Offen. 2,415,402 and Germ. Offen. 2,436,686, an English language abstract of which is

disclosed in Chem. Abs. 82, 31343m (1975) and Chem. Abs. 83, 10556 p (1975), respectively.

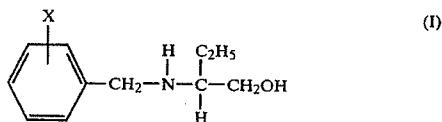
SUMMARY OF THE INVENTION

In accordance with the present invention there is provided a process for resolving DL-Mandelic acid which comprises reacting at moderately elevated temperatures in a two-phase liquid mixture of water and a suitable water-immiscible organic solvent about equimolecular amounts of DL-Mandelic acid and an optically active 2-benzylamino-1-butanol, represented by formula (I), to form a crude mandelate salt, represented by formula (II),

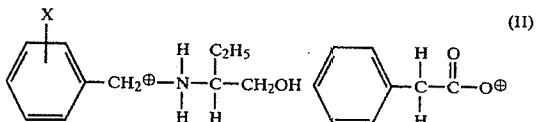


wherein X is as previously defined; said crude mandelate salt is recovered and purified by contact with a suitable solvent to obtain an optically pure mandelate salt, represented by formula (II); the optically active mandelate salt is hydrolyzed with aqueous sodium or potassium hydroxide in a two-phase liquid mixture to obtain an organic phase containing an optically active compound of formula (I) and an alkalized aqueous phase containing the sodium or potassium salt of an optically active mandelic acid. The latter is acidified and an optically active mandelic acid is recovered therefrom. This process comprises the following steps:

(a) reacting about equimolecular amounts of DL-mandelic acid and an optically active 2-benzylamino-1-butanol represented by formula (I),



wherein X represents chloro, bromo, fluoro, or nitro, at moderately elevated temperatures in a two-phase mother liquor consisting of a mixture of an aqueous phase and an organic phase, said organic phase being a lower alkyl ester of a lower aliphatic carboxylic acid selected from ethyl acetate, n-propyl acetate, isopropyl acetate, ethyl propionate, n-propyl propionate, or isopropyl propionate, or mixtures thereof, to form a mandelate salt represented by formula (II),



(b) cooling the reaction mixture to crystallize said mandelate salt;

(c) separating the crude mandelate salt from the two-phase mother liquor;

(d) recrystallizing or slurring the crude mandelate salt in a solvent medium selected from water, methanol, ethanol, or isopropanol, or mixtures thereof, to obtain an optically pure mandelate salt;

(e) alkalinizing the aqueous phase of the two-phase mother liquor obtained in step (c);

(f) separating the alkalinized aqueous phase from the organic phase;

(g) agitating the optically pure mandelate salt from step (d) and the organic phase from step (f) with about 1.05 to 1.10 moles of aqueous sodium or potassium hydroxide per mole of mandelate salt at ambient temperature to hydrolyze said salt and form a clear two-phase liquid mixture consisting of an organic phase containing an optically active compound of formula (I) and an alkalinized aqueous phase containing the sodium or potassium salt of an optically active mandelic acid;

(h) recovering the aqueous phase from step (g) and reacting said salt of an optically active mandelic acid with about an equimolecular amount of an organic dicarboxylic acid selected from oxalic, tartaric, maleic, malonic, or fumaric acid, at ambient or slightly elevated temperature to form a mixture of an optically active mandelic acid and a mono-sodium or potassium salt of said dicarboxylic acid having a low solubility in water;

(i) cooling the reaction mixture to ambient temperature and diluting the same with a water-soluble organic liquid solvent selected from acetone, methanol, ethanol, n-propanol, or isopropanol to complete the precipitation of said salt of said dicarboxylic acid;

(j) separating said salt of said dicarboxylic acid;

(k) removing said water-soluble organic solvent; and

(l) recovering D-($-$) or L-($+$)-mandelic acid from said mother liquor.

In the preferred embodiment of this invention X represents chloro, bromo, or fluoro and the water-immiscible organic solvent is a lower alkyl ester of a lower aliphatic acid selected from ethyl acetate, n-propyl acetate, isopropyl acetate, ethyl propionate, n-propyl propionate or isopropyl propionate. The process of the preferred embodiment comprises performing the steps described in the above paragraph wherein step (a) is reacting equimolecular amounts of DL-mandelic acid and a compound of formula (I) wherein X represents chloro, bromo, or fluoro at a temperature of about 40°–50° C. in a mixture of water and isopropyl acetate; step (b) is cooling to a temperature of about 0°–25° C. over a period of about 1–2 hours; step (d) is slurring 45 said crude mandelate salt in water at an ambient or slightly elevated temperature and then cooling it to about 0°–20° C.; step (e) is alkalinizing the aqueous phase of said two-phase mother liquor to a pH of at least 12; step (g) is agitating said optically pure mandelate salt 50 and said organic phase with an amount of 50% by weight aqueous sodium hydroxide to provide between about 5–10% molecular excess of said sodium hydroxide after complete hydrolysis of said mandelate salt; step (h) is reacting said salt of an optically active mandelic acid with an equimolecular amount of oxalic acid at a 55 temperature of about 25°–40° C.; and step (i) is cooling the reaction mixture to a temperature of about 20°–25° C. diluting the same with acetone to complete the precipitation of monosodium oxalate and cooling the essentially acetone-free mother liquor to a temperature of about 0°–10° C. to crystallize D-($-$) or L-($+$)-mandelic acid.

In the especially preferred embodiment of this invention the compound of formula (I) is D-($-$)-2-(4-chlorobenzylamino)-1-butanol, and the water-immiscible organic solvent is isopropyl acetate. The process of the especially preferred embodiment comprises per-

forming the steps described in the above two paragraphs wherein step (a) is reacting about equimolecular amounts of DL-mandelic acid and D-($-$)-2-(4-chlorobenzylamino)-butanol; step (b) is cooling to a temperature of about 5°–10° C.; step (d) is slurring said crude mandelate salt at a temperature of about 25°–30° C. and cooling it to about 5°–10° C. to obtain D-($-$)-2-(4-chlorobenzylamino)-1-butanol-($-$)-mandelate; step (e) is alkalinizing said aqueous phase to a pH of about 13; step (g) is agitating said D-($-$)-2-(4-chlorobenzylamino)-1-butanol-($-$)-mandelate and said organic phase; step (h) is reacting at a temperature of about 30°–35° C.; and step (i) is cooling the reaction mixture to a temperature of about 20°–25° C. and diluting the same with acetone to complete the precipitation of monosodium oxalate and cooling the essentially acetone-free mother liquor to a temperature of about 0°–5° C. to crystallize D-($-$)-mandelic acid.

The process of this invention is characterized by a unique two-phase liquid reaction medium which lends itself to the recovery of the crude mandelate salt, and the recovery and recycling of the optically active 2-benzylamino-1-butanol and unreacted mandelic acid.

In an alternative embodiment, this process comprises the steps described in the above paragraphs wherein step (f) is separating the alkalinized aqueous phase from the organic phase, heating said aqueous phase at reflux temperature until racemization is complete and acidifying the resulting solution.

In a further alternative embodiment, this process comprises the steps described in the above paragraphs wherein step (f) is separating the alkalinized aqueous phase from the organic phase, heating said aqueous phase at reflux temperature until racemization is complete and acidifying the resulting solution, and in a still further alternative embodiment, the DL-mandelic acid used in step (a) is obtained from the racemized aqueous phase of step (f).

In a final alternative embodiment, this process comprises the steps described in the above paragraphs wherein the optically active 2-(benzylamino)-1-butanol used in step (a) is obtained from said organic phase containing an optically active compound of formula (I) of step (g).

DESCRIPTION OF PREFERRED EMBODIMENTS

The process of this invention may be divided into the following stages:

- (1) the formation and isolation of a crude 2-benzylamino-1-butanol mandelate salt represented by formula (II),
- (2) the purification of the crude mandelate salt to obtain an optically pure mandelate salt also represented by formula (II),
- (3) the hydrolysis of the optically pure mandelate salt to form a sodium or potassium salt of an optically active mandelic acid, and
- (4) the recovery of an optically active mandelic acid from the solution containing said sodium or potassium salt.

The above-mentioned stages are described below in detail.

(1) Formation and Isolation of Crude Mandelate Salt

An aqueous solution containing about 4–17% by weight, preferably about 8–13%, of DL-Mandelic acid is agitated with a suitable water-immiscible organic

solvent, in which the compound of formula (I) is soluble, preferably a lower alkyl ester of a lower aliphatic carboxylic acid, such as isopropyl acetate. About 1-3 parts by volume, preferably about 1.25-1.5 parts by volume, of organic solvent are employed per part by volume of aqueous solution.

About an equimolecular amount of a compound of formula (I) is added and the reaction mixture is heated to about 40°-55° C., preferably about 45°-50° C., and then cooled to about 0°-20° C., preferably about 5°-10° C., over a period of about 1-3 hours, preferably about 1-2 hours, to precipitate the desired mandelate salt. Preferably, the reaction mixture is seeded at about 20°-35° C. with a few crystals of the desired mandelate salt to induce crystallization. The crystals are then recovered and washed successively with the water-immiscible organic solvent and water at ambient temperatures. The washings are combined with the two-phase mother liquor.

Suitable water-immiscible organic solvents which may be used in the process of this invention include ethyl acetate, n-propyl acetate, isopropyl acetate, ethyl propionate, and n-propyl propionate, or mixtures thereof. The preferred organic solvent is isopropyl acetate.

The aqueous solution of DL-Mandelic acid may be prepared by acidifying a solution of sodium DL-mandelate to a pH of about 1.5-4.0, preferably about 1.8-3.8, at about ambient temperature.

Suitable inorganic acids which may be used in the acidification include concentrated hydrochloric acid, about 40-70% sulfuric acid, phosphoric, concentrated hydrobromic acid, and the like.

Illustrative examples of compounds of formula (I) which may be used in the process of this invention include the following:

D-(--)- or L-(+)-2-(4-chlorobenzylamino)-1-butanol,
D-(--)- or L-(+)-2-(4-bromobenzylamino)-1-butanol,
D-(--)- or L-(+)-2-(4-fluorobenzylamino)-1-butanol,
D-(--)- or L-(+)-2-(3-chlorobenzylamino)-1-butanol,
D-(--)- or L-(+)-2-(3-fluorobenzylamino)-1-butanol,
D-(--)- or L-(+)-2-(3-bromobenzylamino)-1-butanol,
D-(--)- or L-(+)-2-(2-chlorobenzylamino)-1-butanol,
D-(--)- or L-(+)-2-(2-bromobenzylamino)-1-butanol,
D-(--)- or L-(+)-2-(2-fluorobenzylamino)-1-butanol,
D-(--)- or L-(+)-2-(4-nitrobenzylamino)-1-butanol,
D-(--)- or L-(+)-2-(3-nitrobenzylamino)-1-butanol,
D-(--)- or L-(+)-2-(2-nitrobenzylamino)-1-butanol,

(2) Purification of Crude Mandelate Salt

The crude mandelate salt of (1) may be purified by recrystallizing it from a suitable solvent such as water or a water-miscible organic solvent such as methanol, ethanol, or isopropanol, or mixtures thereof. Preferably, the purification is carried out by slurring about 1.5-2 parts by weight of water with one part by weight of crude mandelate at about 25°-55° C., preferably about 25°-30° C., and cooling the slurry to about 0°-20° C., preferably about 5°-10° C., to crystallize the desired optically active mandelate salt. The crystals are then recovered, rinsed with ice cold water (about 3°-5° C.) and dried to obtain the mandelate salt in a yield about 84% of theoretical based on starting material.

The mother liquor and wash liquor from the purification is combined with the two-phase liquid mixture obtained in (1) and alkalized with sodium or potassium hydroxide, preferably sodium hydroxide, to increase

the pH of the aqueous layer to at least 12, preferably about 13.

The alkalinized aqueous phase, now containing the sodium or potassium salt of the undesired mandelic acid, is separated and reserved for subsequent racemization.

The organic phase is reserved for the hydrolysis step. Optionally the organic phase can be washed with water before hydrolyzing.

10 (3) Hydrolysis of Optically Active Mandelate Salt

The purified mandelate salt from (2) is agitated with the organic phase recovered in (2), preferably isopropyl acetate, and an aqueous solution of an alkalinizing agent, preferably a dilute solution of caustic soda containing about 1.05-1.10 moles of sodium hydroxide per mole of mandelate salt, at about 20°-30° C., preferably about 25°-30° C., until the two-phase mixture becomes clear. The aqueous phase now contains an alkali salt of the desired mandelic acid and the organic phase contains practically all of the compound of formula (I) charged in (1).

The aqueous phase is recovered and optionally reextracted with additional water-immiscible organic solvent, preferably isopropyl acetate.

25 (4) Recovery of Optically Active Mandelic Acid

The aqueous phase from (3) is stirred with about an equimolecular amount of a suitable dicarboxylic acid, preferably oxalic acid dihydrate, at about 25°-50° C., preferably about 30°-35° C., to form a solution containing the desired optically active mandelic acid. The solution is cooled to ambient temperature to precipitate an alkali acid salt, preferably sodium acid oxalate, therefrom. The resulting slurry is then diluted with a water-miscible organic solvent to complete the precipitation of the alkali acid salt.

Suitable dicarboxylic acids which may be used include oxalic acid dihydrate, tartaric, maleic, fumaric and malonic acids, and the like.

40 Suitable water-miscible organic solvents which may be used include methanol, ethanol, isopropanol, n-propanol or acetone, or mixtures thereof. The preferred diluent is acetone. Generally about 1-3 volumes of diluent are employed per volume of aqueous solution.

The alkali acid salt is separated and the mother liquor is heated to distil off the water-miscible organic solvent. The residual solution is then cooled to about 0°-10° C., preferably about 0°-5° C., stirred thereto for about one hour and filtered. The crystals are rinsed with ice cold 50 water, about 3°-5° C., and dried to obtain D-(--) or L-(+)-mandelic acid. The overall yield from (1) is about 60% of theoretical. Further amounts of the optically active mandelic acid can be recovered by concentrating the aqueous filtrate.

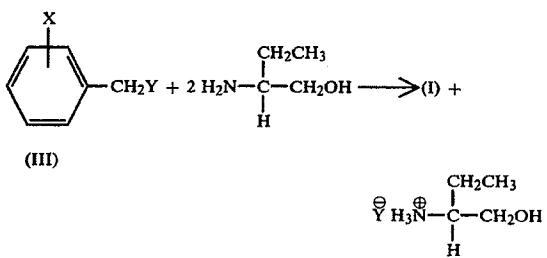
55 Racemization and Recovery of DL-Mandelic Acid

The alkalinized aqueous phase from (2) which contains the sodium or potassium salt of the undesired mandelic acid is further alkalinized by the addition thereto of about two moles of additional sodium or potassium hydroxide per mole of mandelic acid therein. The reaction mixture is then heated at reflux until racemization is completed, as indicated by a zero optical rotation. The reaction mixture is then neutralized to pH 7 by the addition of concentrated hydrochloric acid and at least an equivalent amount of calcium chloride is added. The resulting calcium DL-mandelate which precipitates is recovered by filtration, washed with water and reacted in water

with an equimolecular amount of sodium carbonate. The precipitated calcium carbonate is recovered by filtration and the resulting filtrate containing sodium DL-mandelate is acidified, as previously described, and recycled in (1).

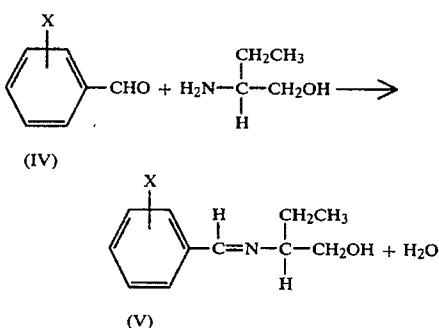
The calcium DL-mandelate may also be reacted in water with an equimolecular amount of a dicarboxylic acid such as oxalic acid dihydrate, tartaric, maleic, fumaric, and malonic acids, and the like, to form an insoluble calcium salt of the dicarboxylic acid and an aqueous solution containing DL-mandelic acid. The insoluble salt is separated by filtration and the aqueous filtrate is recycled in (1).

The optically active 2-(benzylamino)-1-butanol compounds used in this invention may be prepared by two methods. In one method, an optically active form of 2-amino-1-butanol is reacted with an appropriate benzyl halide (III), as illustrated below, wherein X is as previously defined, and Y is a halogen atom, such as chloro, bromo, or fluoro.

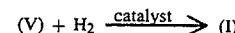


In the above reaction sufficient excess (+)- or (-)-2-amino-1-butanol is employed to react with any hydrogen halide generated in the reaction. The reaction is carried out by adding the benzyl halide in portions to the (+)- or (-)-2-amino-1-butanol at about 60° to 80° C. over a period of about 30 minutes while stirring and then maintaining the temperature between 60° and 85° C. for about 1 to 5 hours after completion of the addition. The reaction mixture is then added to aqueous caustic to precipitate the product. The crude product is filtered and recrystallized from a suitable solvent such as isopropanol, acetone, toluene, mixtures of isopropanol and water, and the like, to obtain the desired optically pure product.

In another method, either d- or L-2-amino-1-butanol is reacted with an appropriate benzaldehyde (IV) to give an intermediate Schiff base (V), which is subsequently catalytically reduced to the desired optically active 2-(benzylamino)-1-butanol, as illustrated below, wherein X is as previously defined.



-continued



5 The preparation of dextrorotatory 2-amino-1-butanol is described by Halmos et al. in U.S. Pat. No. 3,553,257. The preparation of levorotatory 2-amino-1-butanol is described in Beilstein 4, 291.

10 The following examples further illustrate the invention. All parts and percentages are by weight unless otherwise specified.

Unless otherwise indicated, optical rotations were measured by dissolving 1.25, 2.5, 3.0, 4.0, or 5.0 grams of the compound in 100 mls. of methanol and determining the rotation of the plane of a sodium D line at 25° C.

EXAMPLE 1

Formation and Isolation of D-(-)-2-(4-Chlorobenzylamino)-1-Butanol-(--)-Mandelate

A stirred mixture of DL-mandelic acid (152 grams; 0.999 mole), 750 mls of water, 1000 mls of isopropyl acetate and D-(-)-2-(4-chlorobenzylamino)-1-butanol (213 grams; 0.997 mole) is heated to 45° C. to effect clarification, slowly cooled to 25° C., seeded with D-(-)-2-(4-chlorobenzylamino)-1-butanol (-)-mandelate and slowly cooled to 5° C. over a period of about 2 hours to crystallize D-(-)-2-(4-chlorobenzylamino)-1-butanol (-)-mandelate from the reaction mixture. The crystals are recovered by filtration, washed with 100 mls of isopropyl acetate (25° C.) and 100 mls of water (25° C.), and dried to obtain 179.1 grams of crude product.

35 The crude product is slurried in 300 mls of water (50° C.) and the resulting slurry is cooled to 5° C. and filtered. The recovered crystals are washed with 50 mls of water (5° C.) and dried to obtain 153.6 grams (84% of theoretical) of pure D-(-)-2-(4-chlorobenzylamino)-1-butanol-(--)-mandelate, $[\alpha]_D^{25} = -36.25^\circ$ (C=4; in methanol).

40 The two-phase filtrate and wash liquors obtained from the filtration of the crude product are combined with the filtrate and wash liquors obtained from the isolation of the pure product and shaken with 15 mls of 50% aqueous sodium hydroxide at room temperature until clear. The mixture is allowed to settle and the aqueous layer, about 1020 mls, containing the sodium salt of L-(+)-mandelic acid, is separated. This solution is saved for subsequent racemization. The isopropyl acetate layer is utilized in Example 2.

45 In the manner described above substituting ethyl acetate, n-propyl acetate, ethyl propionate, n-propyl propionate, or isopropyl propionate, or mixtures thereof, for the isopropyl acetate similar results are obtained.

EXAMPLE 2

Hydrolysis of D-(-)-2-(4-Chlorobenzylamino)-1-Butanol (-)-Mandelate

The isopropyl acetate layer from Example 1 is mixed with D-(-)-2-(4-chlorobenzylamino)-1-butanol (-)-mandelate (152.6 grams; 0.42 mole) and 172 mls of 10% 60 aqueous sodium hydroxide, shaken at 30° C. until clarified, and allowed to settle. The aqueous layer, which contains sodium D-(-)-mandelate, is separated and saved for subsequent processing. The organic layer is

washed twice with 15 mls of water and the aqueous washings are combined with the above-mentioned aqueous layer.

The water-washed isopropyl acetate layer, now containing about 0.99 mole of D-(*-*)-2-(4-chlorobenzylamino)-1-butanol is saved for recycling in Example 5.

EXAMPLE 3

Isolation of D-(*-*)-Mandelic Acid

The combined aqueous layer and washings, containing the sodium D-(*-*)-mandelate from Example 2, is reacted with oxalic acid dihydrate (53 grams; 0.42 mole) at 50° C. to form sodium acid oxalate which crystallizes from the solution. The resulting slurry is diluted with 400 mls of acetone, cooled to 25° C., and allowed to stand for 2 hours to complete the crystallization. The slurry is filtered to separate the sodium acid oxalate which is then washed with 80 mls of acetone and dried.

The filtrate is combined with the acetone wash liquor, concentrated to about 200 mls and then cooled to 5° C. to crystallize the D-(*-*)-mandelic acid. The resulting slurry is filtered and the solid is washed with 50 mls of water (5° C.) and dried to obtain 45.5 grams (71.2% of theoretical) of D-(*-*)-mandelic acid: m.p. 131°-133° C.; $[\alpha]_D^{25} = -153.8^\circ$ (C, 4 in water). The overall yield from the D, L-mandelic acid is 59.9% of theoretical.

In the manner of Example 3 substituting equimolecular amounts of tartaric, maleic, fumaric, or malonic acid for the oxalic acid similar results are obtained.

In the manner of Example 3 substituting methanol, ethanol, n-propanol or isopropanol for the acetone similar results are obtained.

EXAMPLE 4

Racemization of Sodium L-(+)-Mandelate

The aqueous solution of sodium L-(+)-mandelate from Example 1 is mixed with 45 mls of 50% aqueous sodium hydroxide, heated to boiling and concentrated to about 1100 mls, then refluxed for 20 hours. At the end of this period the sodium L-(+)-mandelate is completely racemized; $[\alpha]_D^{25} = 0^\circ$ (C, 4 in water).

The solution is then neutralized to pH 7 by adding concentrated hydrochloric acid thereto, and reacted at 50° C. by slowly adding a solution of calcium chloride monohydrate (33 grams; 0.255 mole) in 20 mls of water. The resulting reaction mixture is cooled to 25° C. and

filtered to recover the solid. The recovered solid is washed free of chloride ion with water and dried to obtain 79 grams (92.3% of theoretical) of calcium D, L-mandelate.

5 The racemic calcium mandelate, which is equivalent to 0.46 mole of D, L-mandelic acid, is reacted with oxalic acid dihydrate (29 grams; 0.23 mole) in 500 mls of water at 55° C. to form calcium oxalate which crystallizes out. The resulting slurry is cooled to 25° C. and the calcium oxalate is separated by filtration and washed with 250 mls of water. The filtrate, which now contains about 0.46 mole of D, L-mandelic acid is combined with the water wash liquor and saved for use in Example 5.

EXAMPLE 5

Recycle of D, L-Mandelic Acid and D-(*-*)-2-(4-Chlorobenzylamino)-1-Butanol

The water-washed isopropyl acetate solution from Example 2, containing about 0.99 mole of recovered D-(*-*)-2-(4-chlorobenzylamino)-1-butanol, is mixed with the filtrate plus water wash from Example 4, containing 0.46 mole of D, L-mandelic acid, and fresh D, L-mandelic acid (82 grams; 0.54 mole) is added thereto. The mixture is stirred at 30° C. until clarified, seeded with D-(*-*)-2-(4-chlorobenzylamino)-1-butanol. (*-*) mandelate, slowly cooled to 10° C. over 1½ hours and filtered. The crystals are washed with 125 mls of isopropyl acetate and 250 mls of water, and dried to obtain 163 grams of crude D-(*-*)-2-(4-chlorobenzylamino)-1-butanol (*-*) mandelate.

30 The crude product is slurried in 250 mls of water at 55° C. and the slurry is cooled to 10° C. and filtered. The recovered crystals are washed with 50 mls of water (5° C.) and dried to obtain 153.6 grams (84% of theoretical) of D-(*-*)-2-(4-chlorobenzylamino)-1-butanol (*-*) mandelate, $[\alpha]_D^{25} = -35.75^\circ$ (C, 4 in methanol).

EXAMPLES 6-28

40 In the manner described in Example 1 substituting 0.997 mole of the appropriate 2-(benzylamino)-1-butanol for D-(*-*)-2-(4-chlorobenzylamino)-1-butanol the optically active mandelate salts of Table I are prepared. Hydrolysis of the mandelate salt in the manner of Example 2 and isolation in the manner of Example 3 is productive of D-(*-*) or L-(+)-mandelic acid, depending on the salt selected.

TABLE I

Example	Starting 2-(Benzylamino)-1-Butanol	Product
6	D-(<i>-</i>)-2-(4-fluorobenzylamino)-1-butanol	D-(<i>-</i>)-2-(4-fluorobenzylamino)-1-butanol-(<i>-</i>)-mandelate
7	L-(+)-2-(4-chlorobenzylamino)-1-butanol	L-(+)-2-(4-chlorobenzylamino)-1-butanol-(+)-mandelate
8	L-(+)-2-(4-bromobenzylamino)-1-butanol	L-(+)-2-(4-bromobenzylamino)-1-butanol-(+)-mandelate
9	D-(<i>-</i>)-2-(3-chlorobenzylamino)-1-butanol	D-(<i>-</i>)-2-(3-chlorobenzylamino)-1-butanol-(<i>-</i>)-mandelate
10	L-(+)-2-(3-chlorobenzylamino)-1-butanol	L-(+)-2-(3-chlorobenzylamino)-1-butanol-(+)-mandelate
11	D-(<i>-</i>)-2-(3-bromobenzylamino)-1-butanol	D-(<i>-</i>)-2-(3-bromobenzylamino)-1-butanol-(<i>-</i>)-mandelate
12	L-(+)-2-(3-bromobenzylamino)-1-butanol	L-(+)-2-(3-bromobenzylamino)-1-butanol-(+)-mandelate
13	D-(<i>-</i>)-2-(3-fluorobenzylamino)-1-butanol	D-(<i>-</i>)-2-(3-fluorobenzylamino)-1-butanol-(<i>-</i>)-mandelate
14	L-(+)-2-(3-fluorobenzylamino)-1-butanol	L-(+)-2-(3-fluorobenzylamino)-1-butanol-(+)-mandelate
15	D-(<i>-</i>)-2-(2-fluorobenzylamino)-1-butanol	D-(<i>-</i>)-2-(2-fluorobenzylamino)-1-butanol-(<i>-</i>)-mandelate
16	L-(+)-2-(2-fluorobenzylamino)-1-butanol	L-(+)-2-(2-fluorobenzylamino)-1-butanol-(+)-mandelate
17	D-(<i>-</i>)-2-(2-chlorobenzylamino)-1-butanol	D-(<i>-</i>)-2-(2-chlorobenzylamino)-1-butanol-(<i>-</i>)-mandelate
18	L-(+)-2-(2-chlorobenzylamino)-1-butanol	L-(+)-2-(2-chlorobenzylamino)-1-butanol-(+)-mandelate
19	D-(<i>-</i>)-2-(2-bromobenzylamino)-1-butanol	D-(<i>-</i>)-2-(2-bromobenzylamino)-1-butanol-(<i>-</i>)-mandelate
20	L-(+)-2-(2-bromobenzylamino)-1-butanol	L-(+)-2-(2-bromobenzylamino)-1-butanol-(+)-mandelate
21	D-(<i>-</i>)-2-(4-nitrobenzylamino)-1-butanol	D-(<i>-</i>)-2-(4-nitrobenzylamino)-1-butanol-(<i>-</i>)-mandelate
22	L-(+)-2-(4-nitrobenzylamino)-1-butanol	L-(+)-2-(4-nitrobenzylamino)-1-butanol-(+)-mandelate
23	D-(<i>-</i>)-2-(3-nitrobenzylamino)-1-butanol	D-(<i>-</i>)-2-(3-nitrobenzylamino)-1-butanol-(<i>-</i>)-mandelate
24	L-(+)-2-(3-nitrobenzylamino)-1-butanol	L-(+)-2-(3-nitrobenzylamino)-1-butanol-(+)-mandelate
25	D-(<i>-</i>)-2-(2-nitrobenzylamino)-1-butanol	D-(<i>-</i>)-2-(2-nitrobenzylamino)-1-butanol-(<i>-</i>)-mandelate
26	L-(+)-2-(2-nitrobenzylamino)-1-butanol	L-(+)-2-(2-nitrobenzylamino)-1-butanol-(+)-mandelate
27	L-(+)-2-(4-fluorobenzylamino)-1-butanol	L-(+)-2-(4-fluorobenzylamino)-1-butanol-(+)-mandelate

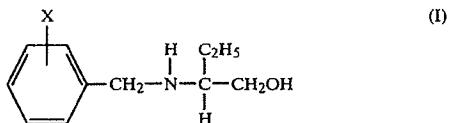
TABLE I-continued

Example	Starting 2-(Benzylamino)-1-Butanol	Product
28	D-(—)2-(4-bromobenzylamino)-1-butanol	D-(—)2-(4-bromobenzylamino)-1-butanol-(—)-mandelate

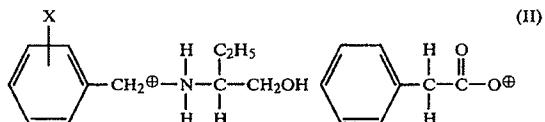
I claim:

1. A process for resolving DL-mandelic acid which comprises:

(a) reacting about equimolecular amounts of DL-mandelic acid and an optically active 2-benzylamino-1-butanol represented by formula (I),



wherein X represents chloro, bromo, fluoro, or nitro, at about 40°-50° C. in a two-phase mother liquor, consisting of a mixture of a water phase and a water immiscible organic phase, said organic phase being a lower alkyl ester of a lower aliphatic carboxylic acid selected from ethyl acetate, n-propyl acetate, isopropyl acetate, ethyl propionate, n-propyl propionate, or isopropyl propionate, or mixtures thereof, to form a mandelate salt represented by formula (II),



- (b) cooling the reaction mixture to crystallize said mandelate salt;
- (c) separating the crude mandelate salt from the two-phase mother liquor;
- (d) recrystallizing or slurrying the crude mandelate salt in a solvent medium selected from water, methanol, ethanol, or isopropanol, or mixtures thereof, to obtain an optically pure mandelate salt;
- (e) alkalizing the water phase of the two-phase mother liquor obtained in step (c);
- (f) separating the alkalized water phase from the organic phase;
- (g) agitating the optically pure mandelate salt from step (d) and the organic phase from step (f) with about 1.05 to 1.10 moles of aqueous sodium or potassium hydroxide per mole of mandelate salt at ambient temperature to hydrolyze said salt and form a clear two-phase liquid mixture consisting of an organic phase containing an optically active compound of formula (I) and an alkalized aqueous phase containing the sodium or potassium salt of an optically active mandelic acid;
- (h) recovering the aqueous phase from step (g) and reacting said salt of an optically active mandelic acid with about an equimolecular amount of an organic dicarboxylic acid selected from oxalic, tartaric, maleic, malonic, or fumaric acid, at about 25°-40° C. to form a mixture of an optically active mandelic acid and a mono-sodium or potassium salt of said dicarboxylic acid having a low solubility in water;
- (i) cooling the reaction mixture to ambient temperature and diluting the same with a water-soluble

organic liquid solvent selected from the group consisting of acetone, methanol, ethanol, n-propanol, and isopropanol to complete the precipitation of said salt of said dicarboxylic acid;

(j) separating said salt of said dicarboxylic acid;

(k) removing said water-soluble organic solvent; and

(l) recovering D-(—) or L-(+)-mandelic acid from said mother liquor.

10 2. The process of claim 1 wherein step (a) is reacting about equimolecular amounts of DL-mandelic acid and a compound of formula (I) wherein X represents chloro, bromo, or fluoro at a temperature of about 40°-50° C. in a mixture of water and isopropyl acetate; 15 step (b) is cooling to a temperature of about 0°-25° C. over a period of about 1-2 hours; step (d) is slurrying said crude mandelate salt in water at about 25°-30° C. and then cooling it to about 0°-20° C.; the step (e) is alkalizing the water phase of said two-phase mother 20 liquor to a pH of at least 12; step (g) is agitating said optically pure mandelate salt and said organic phase with an amount of 50% by weight aqueous sodium hydroxide to provide between about a 5-10% molecular excess of said sodium hydroxide after complete hydrolysis of said mandelate salt; step (h) is reacting said salt of an optically active mandelic acid with an equimolecular amount of oxalic acid at a temperature of about 25°-40° C.; and step (i) is cooling the reaction mixture to a temperature of about 20°-25° C. and diluting the same 25 with acetone to complete the precipitation of monosodium oxalate and cooling the essentially acetone-free mother liquor to a temperature of about 0°-10° C. to crystallize D-(—) or L-(+)-mandelic acid.

30 3. The process of claim 2 wherein step (a) is reacting about equimolecular amounts of DL-mandelic acid and D-(—)2-(4-chlorobenzylamino)-butanol; step (b) is cooling to a temperature of about 5°-10° C.; step (d) is slurrying said crude mandelate salt at a temperature of about 25°-30° C. and the cooling it to about 5°-10° C. to obtain D-(—)2-(4-chlorobenzylamino)-1-butanol-(—)-mandelate; step (e) is alkalizing said water phase to a pH of about 13; step (g) is agitating said D-(—)2-(4-chlorobenzylamino)-1-butanol-(—)-mandelate and said organic phase; step (h) is reacting at a temperature of about 30°-35° C.; and step (i) is cooling the reaction mixture to a temperature of about 20°-25° C. and diluting the same with acetone to complete the precipitation of monosodium oxalate and cooling the essentially acetone-free mother liquor to a temperature of about 0°-5° C. to crystallize D-(—)-mandelic acid.

35 4. The process of claim 1 wherein step (f) is separating the alkalized water phase from the organic phase, heating said water phase at reflux temperature until racemization is complete and acidifying the resulting solution.

50 5. The process of claim 4 wherein the DL-mandelic acid used in step (a) is obtained from the racemized water phase of step (f).

60 6. The process of claim 1 wherein the optically active 2-(benzylamino)-1-butanol used in step (a) is obtained from said organic phase containing an optically active compound of formula (I) of step (g).

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